REMARKS

The status of the claims is as follows:

Original:	11
Currently amended:	9, 10, 12 and 14
Previously presented:	13, 15 and 16
Canceled:	1-8
Withdrawn:	None
New:	17-25

Claims 9-25 will be pending with entry of this amendment. Reconsideration is requested.

Amendments

Claims 1-8 have been canceled.

Claim 9 has been amended to recite that R^5 = H and to eliminate H as a choice for R^1 and R^{1a}. The definition of R^1 and R^{1a} has also been amended to replace "C_{1-6} alkyl" with "tert-butyl". The definition of R^2 has also been amended to remove the choice of the formation of a "3 to 7 membered carb ocyclic" when the R^2 groups are taken together with any intervening atom. Since the only intervening atom is N, the ring formed by taking the R^2 groups together cannot be a carbocyclic.

Also in claim 9, the term "and" has been replaced with "or" in the list of groups in the definitions of R^1, R^{1a}, R^2, R^{2a}, R^3, R^{3a}, and R^4, to more clearly indicate the groups are alternatives. Minor grammatical changes have also been made in claim 9, and a misspelling ("diasteriomer") corrected.

The list of compounds in dependent claim 10 has been modified to conform with claim 9 as amended.

The definition of R^1 and R^{1a} in dependent claims 12 and 14 has been amended to conform with claim 9 as amended.

Claims 17-25 are new. Exemplary support for the new claims is as follows:

Claim	Support
17	Example 19 on page 22
18 & 25	page 13, lines 27-30; original claim 11
19, 20, 22 & 24	page 10, lines 18-21

21	original claim 6
22	page 10, lines 18-21

None of the foregoing amendments introduces new matter.

Restriction Requirement

The withdrawal of the restriction requirement with rejoinder of Groups I and II is acknowledged.

First Rejection under 35 U.S.C. § 102

Claims 1, 3, 7, 9 11 and 13 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Burckhalter et al., *J. Am. Chem. Soc.* 1946, 8: 1804-1901. Burckhalter discloses 2-[(diethylamino)methyl]-3,5-dimethylphenol (Compound II-24). Claims 1, 3 and 7 have been canceled rendering the rejection moot as applied thereto. Claim 9 has been amended to require that R^1 and R^{1a} are each independently tert-butyl, halo, C_{1-6} alkoxy, C_{3-10} cycloalkyl or trihalovinyl. Burckhalter does not disclose use of the compounds encompassed by claim 9. Claims 10-20 directly or indirectly depend from claim 9 and incorporate all of its limitations and thus are also not disclosed in Burckhalter.

Claim 21 recites a list of compounds, each of which has a tert-butyl or a trichlorovinyl substituent in the 3-position and/or the 5-position of the phenol ring. Burckhalter does not disclose such compounds. Claim 22 depends from claim 21 and incorporates all of its limitations, and thus is also not disclosed in Burckhalter.

Claim 23 recites a method for treating malaria by administration of one of a list of compounds, each of which has a tert-butyl or a trichlorovinyl substituent in the 3-position and/or the 5-position of the phenol ring. Burckhalter does not disclose such compounds. Claims 24 and 25 depend from claim 23 and incorporate all of its limitations. Accordingly, claims 24 and 25 are also not disclosed in Burckhalter.

Withdrawal of this rejection is requested.

Second Rejection under 35 U.S.C. § 102

Claims 1-8 have been rejected under 35 U.S.C. § 102(b) as being anticipated by US 3,794,734 (Cragoe) and by Stokker et al., *J. Med. Chem.* 1980, 23: 1414-1427. Cragoe discloses 2-(aminomethyl)-3,5-di-tert-butylphenol hydrochloride (Example 11). Stokker discloses 2-(aminomethyl)-3,5-dimethylphenol hydrochloride and 2-(aminomethyl)-3,5-di-tert-butylphenyl hydrochloride (Compounds 38 and 39 in Table V).

Claims 1-8 have been canceled rendering the rejection moot. It is further noted that the list of compounds recited in new compound claim 21 does not include the compounds disclosed in Cragoe and in Stokker. Claim 22 depends from claim 21 and includes all of its limitations. Accordingly, claims 21 and 22 are not disclosed in either Cragoe or Stokker.

Withdrawal of this rejection is requested.

Third Rejection under 35 U.S.C. § 102

Claims 1, 3 and 7 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Finn et al., *J. Appl. Chem.* 1951, 1: 182-184. Finn discloses 2-(dimethylaminomethyl)-3,5-dimethylphenol.

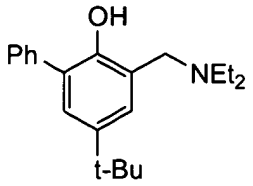
Claims 1, 3 and 7 have been canceled rendering the rejection moot. It is further noted that the list of compounds recited in new compound claim 21 does not include the Finn compound. Claim 22 depends from claim 21 and includes all of its limitations. Accordingly, claims 21 and 22 are not disclosed in Finn.

Withdrawal of this rejection is requested.

First Rejection under 35 U.S.C. § 103

Claims 1-16 have been rejected as being unpatentable over Burckhalter. Claims 1-8 have been canceled rendering the rejection moot as applied thereto. The rejection is traversed with respect to claims 9-16 as amended herein and with respect to new claims 17-25.

Burckhalter directs the person of ordinary skill in the art toward 2-aminoalkylphenols with substituents in the 4- and/or 6-positions. Nearly all of the substituted aminoalkylphenols disclosed in Burckhalter have a non-hydrogen substituent in the 4-position or in the 6-position or in both the 4- and 6-positions of the phenol ring. For example, of the 34 α-amino-*o*-cresols listed in Table II (p.1897), 2 have no substitution on the phenol ring; 4 have a substituent in the 6-position; 9 have a substituent in the 4-position; 11 have 4,6-substitution; 5 have 4,5-substitution; 1 has 3,4,6-substitution; 1 has 3,5,6-substitution; and only one has 3,5-substitution. Burckhalter states (p. 1899, 2nd column under "Pharmacological Results") that of the compounds in Table II, the compound that "proved to be most effective" was Compound II-31 which is a compound with 4,6-substitution; i.e., 4-tert-butyl-6-cyclohexyl-2-[(diethylamino)methyl]phenol. Furthermore, of the 128 compounds disclosed in the reference, the compounds which Burckhalter characterizes as "representative of some of the most interesting types thus far prepared in this particular group" (p. 1901 under the "Summary") are:



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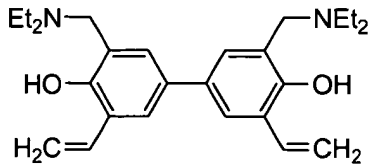

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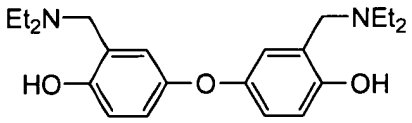
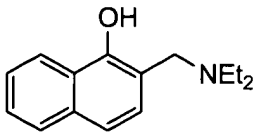


, and


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Three of these four compounds have substituents in either or both the 4- and 6-positions on the phenol ring, and the other compound is a naphthol which is even further removed from the instantly claimed invention.

In contrast to Burckhalter, the malaria treatment methods set forth in instant claims 9-20 require administration of a 2-aminoalkylphenol that has substitution at both the 3- and 5-positions of the phenol ring. Of the very few compounds disclosed in Burckhalter having substituents in the 3- and 5-positions, the closest is 2-[(diethylamino)methyl]-3,5-dimethylphenol (Compound II-24), which lies outside the scope of the instant method claims; i.e., the only alkyl substituent permitted in the 3- and 5-positions of the compounds employed in the instant invention is tert-butyl.

Turning to new claims 21-25, each of the compounds directly or indirectly recited therein has a tert-butyl or a trichlorovinyl group in the 3-position and/or the 5-position of the phenol ring, and has no substitution in the 4- and 6-positions. None of these compounds is disclosed in Burckhalter and, in view of Burckhalter's focus on and preference for compounds having substitution in the 4- and/or 6-positions, none is suggested by Burckhalter.

Withdrawal of this rejection is requested.

Second Rejection under 35 U.S.C. § 103

Claims 1-8 have been rejected as being unpatentable over Cragoe in combination with Stokker. Claims 1-8 have been canceled rendering the rejection moot as applied thereto. The rejection is traversed with respect to new claims 21 and 22.

Cragoe discloses certain 2-aminomethylphenols useful as diuretic, saluretic and antihypertensive agents. Most generally the compounds are of formula I (col. 1, lines 30-40) in which the 4-position of the phenol ring is not hydrogen; i.e., X^2 = halo, lower alkyl, mononuclear aryl, or cycloalkyl (col. 1, lines 46-51). Narrower embodiments are described as the compounds of

formulae Ia (top of col. 2), Ib (bottom of col. 4), and Ic (col. 5, lines 25-30), all of which require a substituent at the 4-position of the phenol ring. Examples 1-24 in Cragoe describe the preparation of specific 2-aminomethylphenols. These compounds are di-, tri-, and tetra-substituted 2-aminomethylphenols, and 23 of the 24 compounds have a substituent at either or both the 4- and the 6-positions. Only the compound disclosed in Example 11 has no substituent at the 4- or 6-position; i.e., it is the HCl salt of 2-aminomethyl-3,5-di-tert-butylphenol. The inclusion of Example 11 in Cragoe is anomalous in that, given the absence of a substituent in the 4-position, it does not appear to be within the scope of the invention as defined and described elsewhere in the document.

The compounds directly and indirectly recited in instant claims 21 and 22 are 2-aminoalkylphenols having substituents at the 3-position and/or the 5-position, and no substitution at either the 4- or the 6-position of the phenol ring. In contrast, Cragoe is directed to mono- or poly-substituted 2-aminomethylphenols in which a substituent is required at the 4-position, except for the 3,5-disubstituted 2-aminomethylphenyl of Example 11, which is not within the scope of claim 21. Cragoe accordingly does not suggest or otherwise guide the person of ordinary skill in the art to the subject matter of claims 21 and 22.

Stokker does not cure the deficiencies of Cragoe. Stokker describes certain 2-aminomethyl-phenols as a new class of saluretic agents. As in Cragoe the focus in Stokker is on 2-aminomethylphenols which have substitution at the 4-position and/or the 6-position of the phenol ring:

- Table IV (p. 1417) lists 6 monosubstituted 2-aminomethylphenols all of which are substituted in the 4-position.
- Table V (pp. 1418-1419) lists 54 disubstituted 2-aminomethylphenols, 2 of which are 3,4-disubstituted, 2 of which are 3,5-substituted, and 50 of which are 4,6-disubstituted.
- Table VI (p. 1420) lists 26 tri-substituted 2-aminomethylphenols, 4 having 3,4,5,-substitution, 17 having 3,4,6-substitution, and 5 having 4,5,6-substitution.
- Table VII (p. 1421) lists 19 3,4,5,6-tetrasubstituted 2-aminomethylphenols.

Only 2 of the 105 compounds disclosed Tables IV-VII in Stokker have no substitution at the 4- or the 6-position. The structure-saluretic activity relationship as described in Stokker (p. 1417, col. 2 and p. 1419, col. 2) is not straightforward and depends upon the number, type and position of the substituents. Nonetheless in discussing the monosubstituted compounds in Table IV, Stokker states that "[a]lthough salycylamine per se is devoid of demonstrable salidiuretic activity, introduction of a chloro or alkyl (except *n*-butyl; cf. **33**) moiety in the 4 position imparts weak activity." (p. 1417, col. 2) And in discussing the disubstituted compounds in Table V, Stokker states that "[a]ppropriate nuclear disubstitution, particularly in the positions 4 and 6, led to

marked enhancement of saluretic activity" (p. 1417, col. 2) Stokker states in the abstract (p. 1414) that "[t]he most active compounds belong to a subseries of 4-alkyl-6-halo derivatives of which [Compound 2 in Table V], 2-(aminomethyl)-4-1,1-dimethyethyl-6-iodophenol, is the most active." It is also noted that the two 3,5-disubstituted compounds in Table V (Compounds 38 and 39) demonstrated no saluretic activity in the dog or the rat.

Considered as a whole, Stokker guides the person of ordinary skill in the art towards substituted 2-aminomethylphenols having a substituent in the 4-position, preferably also having a substituent in the 6-position, and optionally having additional substitution. The reference does not suggest 2-aminoalkylphenols with substitution in the 3- and/or 5-position and no substitution in the 4- and/or 6-positions.

Summarizing, Cragoe alone or in combination with Stokker does not establish a prima facie case of obviousness with respect to claims 21 and 22 and withdrawal of this rejection is requested.

The application is believed to be in condition for allowance and passage to issue is requested. The Examiner is invited to telephone the undersigned should any minor matters need to be resolved before a Notice of Allowance can be mailed.

Respectfully submitted,

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